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Key Words
Ingenol mebutate · Bowen's disease · Dermoscopy · Non-melanoma skin cancers

Abstract
Ingenol mebutate (IM) has recently been approved for the topical treatment of actinic keratoses. It appears to have a dual mechanism of action: rapid necrosis after gel application and a subsequent immune-mediated response, which targets any residual dysplastic epidermal cells. We report the successful treatment of a woman, who had been relapsing into Bowen's disease (BD) on her right forefinger for 8 years. During her clinical history, she had received an allogeneic, HLA-identical stem cell transplant for myeloproliferative syndrome with a JAK2V617F mutation and lobectomy of the pulmonary right lower lobe for adenocarcinoma. We used dermoscopy to monitor the therapeutic response of BD. We discuss IM gel as a possible therapeutic option for BD.

Introduction

Bowen's disease (BD) is a form of in-situ squamous cell carcinoma (SCC). The typical cutaneous non-pigmented BD presents as a slowly growing, well-demarcated erythematous plaque, with an irregular border and surface scaling or crusting that may erode [1, 2]. Dermoscopy is considered a useful method for the diagnosis of BD based on the typical glomerular vessels plus scaly surface and also for monitoring the therapeutic response of BD [3, 4]. The therapeutic approach for BD includes observation alone and topical and surgical treatments [1, 2].

Ingenol mebutate (IM) is a topical drug recently available for the treatment of actinic keratoses (AK) and was approved in Switzerland in June 2013 for this indication [5]. The advantage of IM compared with other topical agents for AK therapy appears to be its dual mechanism of action – a rapid necrosis after only 2 or 3 days' application of IM gel and the subsequent immune-mediated response – which targets any residual dysplastic epidermal cells [6, 7].

We report the case of a 73-year-old woman with non-pigmented BD on her right forefinger, for which we had tried several local and surgical treatments, which had all led to recurrence of the tumour. A local therapy with IM led to a lasting remission of BD.

Case Report

We report the case of a 73-year-old woman with skin phototype III and with a history of a myeloproliferative syndrome positive for a JAK2V617F mutation and osteomyelofibrosis, which had occurred 17 years ago. She was treated with oral thioguanine and splenectomy at first. Eight years after the initial diagnosis, an allogeneic HLA-identical stem cell transplant was performed. During the

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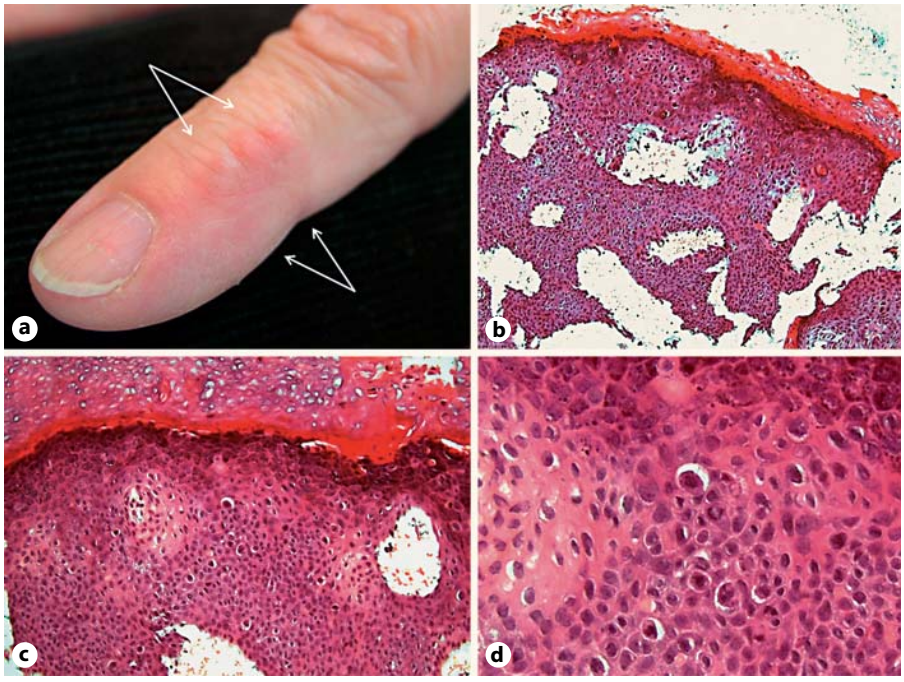

Fig. 1. a Relapsing BD of the right forefinger 5 years after the first diagnosis; **b** shave-excision with full-thickness atypia of the epidermis and parakeratosis. H&E ×100; **c** disorderly maturation of the epidermis with marked atypia and dyskeratotic cells. H&E ×200; **d** dyskeratotic cells and mitoses at different levels in the epidermis. H&E ×400.

2 years after the bone marrow transplant, the patient benefitted from immunosuppressive therapy with oral cyclosporine A. In the following years, she no longer needed any treatment for her hematological disease and did not experience relapse throughout this period. The patient's state of health was satisfactory except that 7 years after the bone marrow transplant she developed an adenocarcinoma of the right lung lower lobe (stage γpT3 γpNO MO), which was successfully removed by right lower pulmonary lobectomy.

One year after stem cell transplant and 9 years after the initial diagnosis, she slowly developed an erythematous plaque on her right forefinger. A skin biopsy was performed and the histological diagnosis was BD. A 5-fluorouracil (5-FU) 5% cream applied twice daily for 3 weeks led to remission of BD, but less than a year later, she relapsed. During the following years, BD was treated with different modalities alternating between 5-FU and imiquimod (IQ) 5% gel, always relapsing a few months after every treatment cycle. This cycle of remission and relapse continued after cyclosporine A had been stopped as well.

We examined the patient for the first time 15 years after the first diagnosis of myeloproliferative syndrome and 6 years after the stem cell transplant. On the distal medial aspect of her right forefinger, she presented an erythematous plaque that overflowed above the line of Wallace measuring 15 × 12 mm (fig. 1a). We performed a shave biopsy in truncal anesthesia. The histological examination confirmed the diagnosis of BD showing full thickness, markedly atypical and dyskeratotic cells of epidermis with mitoses and parakeratosis (fig. 1b–d). Afterward, the patient was treated by a methyl aminolaevulinate (MAL) – photodynamic therapy (PDT). BD relapsed at the lesion edges after 6 months. We therefore treated with IQ 5% cream for 1 month, but BD recurred again 6 months thereafter. One year after the first MAL-PDT, it was treated for a second time.

After a year's relapse of BD at the edges (fig. 2a, b), we decided to perform an off-label treatment with IM 500 μg/g gel, administered once daily for 2 consecutive days, following the clinical course with dermoscopy. At that moment, a treatment with 5-FU 5% cream was refused by the patient, because she complained of pain during previous therapies. Three days after the first application of IM, the skin lesions occurred more reddening and vesicular (fig. 2c). At the dermoscopy examination, the typical glomerular vessels had disappeared, leaving room for an apple juice-like colored picture without vascular structures (fig. 2d). But after 6 weeks, the clinical appearance seemed to have reverted to the same state as before the treatment, which was also confirmed by a dermoscopy where glomerular vessels in the lesion reappeared (fig. 3a, b). With the informed consent of the patient, we decided to treat her with IM 500 μg/g gel, administered once daily for 1 day under occlusion of a patch. The patient complained of pain and a burning sensation a few hours after application of IM. We treated with oral paracetamol 3 times 1 g daily. Following the removal of the patch after 24 h, the symptoms disappeared gradually after 2 days. Three days after the application of IM, vesicular and dyshidrotic skin lesions occurred (fig. 3c). On dermoscopy, the lesions showed a scaly and hyperkeratotic picture with disappearance of the glomerular vessels (fig. 3d). At 6 weeks follow-up, we found clinical remission (fig. 4a) without glomerular vessels on dermoscopy (fig. 4b). Follow-up at 3 months confirmed clinical and dermoscopical remission (fig. 4c, d). At 6 months' follow-up after the second treatment with IM, there had been no relapse with excellent cosmesis.

Discussion

Cutaneous BD is an intra-epidermal skin tumor, presenting as a circumscribed erythematous plaque with scaly or crusted surface or as verrucous or pigmented

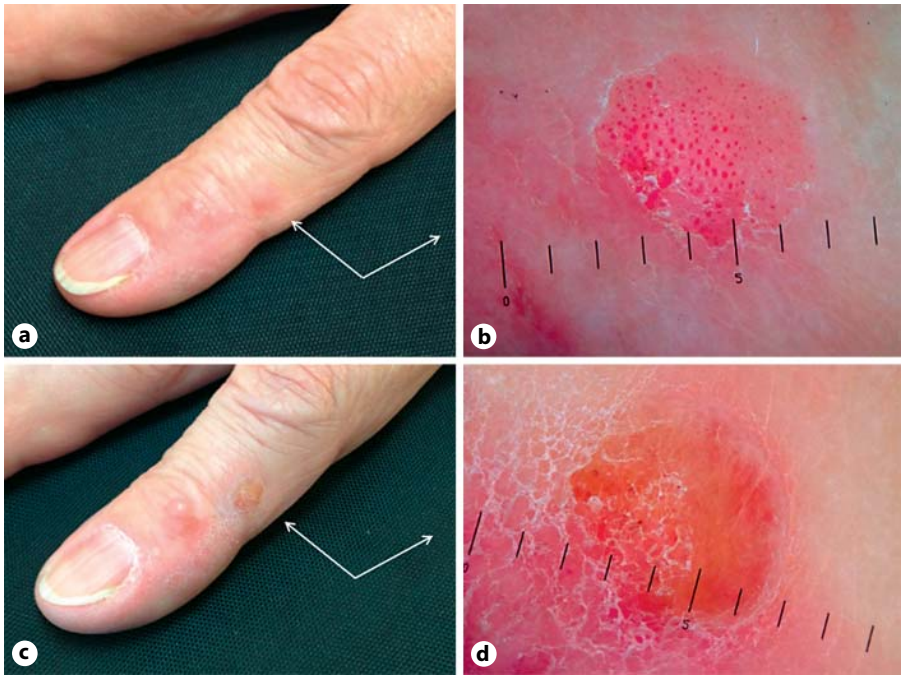

Fig. 2. a Relapsing BD of the right forefinger 8 years after the first diagnosis; **b** dermoscopy of non-pigmented BD showing glomerular vessels that are arranged in clusters and white to yellow scales; **c** after 3 days' treatment with IM, moderate-to-severe reaction is visible with confluent dyshidrotic vesicles; **d** dermoscopy after 3 days' treatment with IM, amorphous erythematous confluent vesicles and white scales.

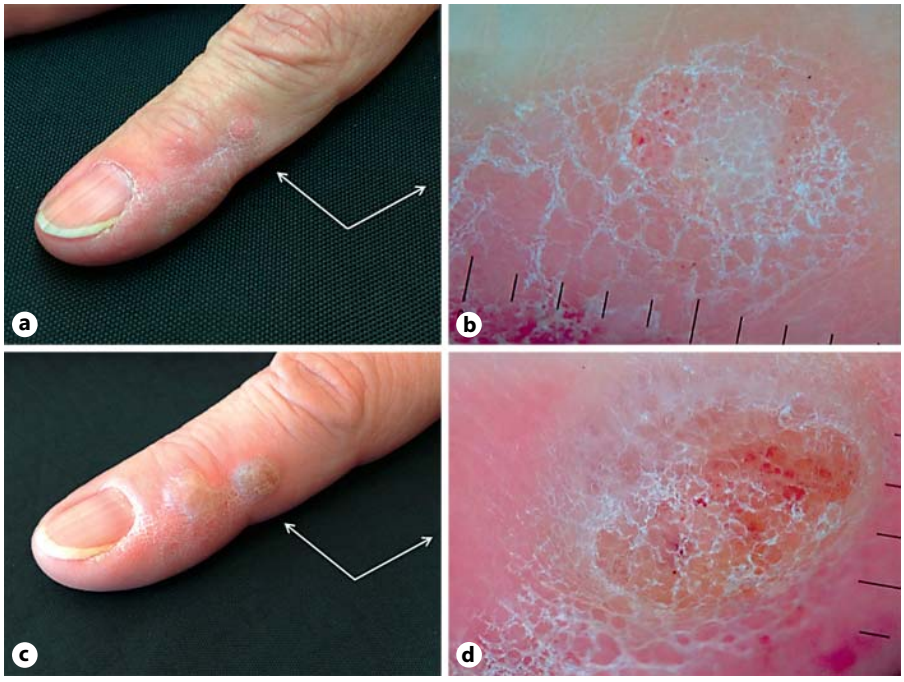

Fig. 3. a Relapsing BD of the right forefinger 6 weeks after the first IM treatment; **b** dermoscopy showing a resurgence of dotted and glomerular vessels associated with marketed white scales; **c** after 3 days' treatment with IM, severe reaction is visible with confluent dyshidrotic vesicles; **d** dermoscopy after 3 days' treatment with IM, amorphous erythematous confluent vesicles and white scales.

variants. The risk of progression to an invasive SCC is small, estimated at 3–5%. Women are most affected (75–85% of the cases). About 3 quarters of tumors are localized in lower extremities. In 80–90% of the patients, the lesion appears solitary. Many etiological factors are discussed: irradiation (solar, photochemotherapy, radiotherapy), arsenic, immunosuppressive diseases or treatments, chronic dermatoses or pre-existent skin lesions and viral-oncogenic human papilloma virus. About 30–50% of the subjects, who developed a BD, also develop or

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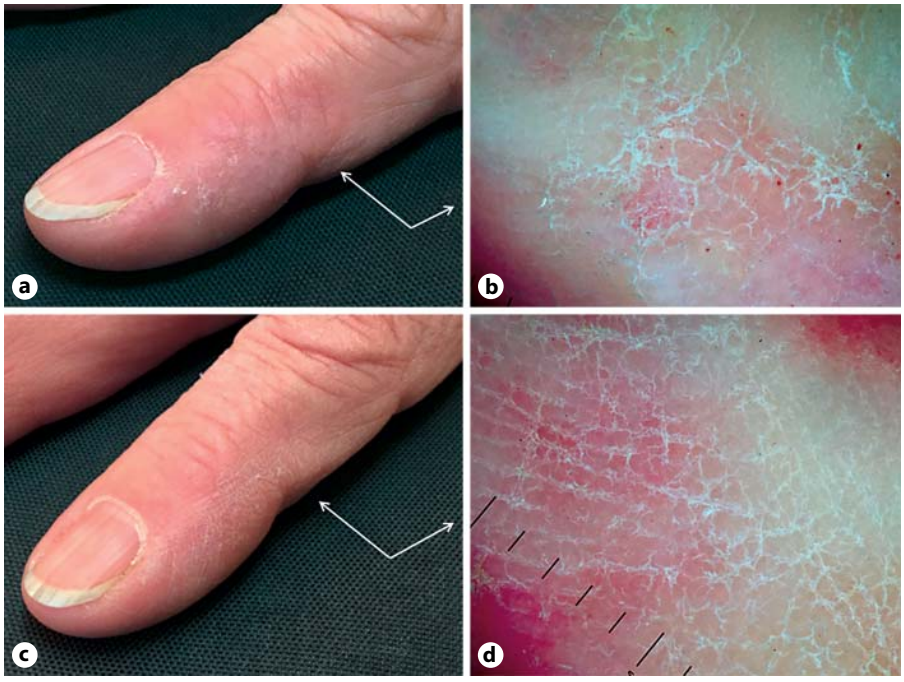

Fig. 4. a The right forefinger 6 weeks after the second IM treatment; **b** dermoscopy not showing a resurgence of dotted and glomerular vessels. White scales; **c** after 3 months' treatment with IM, no BD relapse is visible; **d** dermoscopy after 3 months' treatment with IM, not showing a resurgence of dotted and glomerular vessels.

have developed a non-melanoma skin cancer, probably reflecting common solar damage [1, 2, 8].

The clinical diagnosis of BD is usually confirmed by a biopsy, showing full-thickness epidermal dysplasia without dermal invasion [1, 2, 8]. Micali et al. [9] reviewed, according to evidence-based analysis, therapeutic possibilities for the topical treatment of skin cancers and found 5-FU, IQ, PDT and surgery with documented efficacy.

Dermoscopy is used by dermatologists not only as a non-invasive method for the diagnosis of skin cancers but also to monitor the treatment efficacy in the follow-up. At dermoscopy, non-pigmented BD shows a characteristic morphologic type of dotted and tortuous vessels similar to the glomerular apparatus of the kidneys or arranged in lines at the periphery and opaque, yellow to white scales. Histopathologically, the glomerular vessels correspond to the presence of convolutions of capillaries in the dermal papillae, which are grouped in clusters and are dilated [3, 4, 10–13]. Mun et al. [4] proposed an algorithm for the clinical use of dermoscopy to monitor the therapeutic response of BD: once these vascular structures disappear, the BD is clinically cured. The histopathological examination typically is negative for remains of BD. In these cases, the authors suggested a regular follow-up by dermoscopy. If on dermoscopy the glomerular vessels persist, a histopathological assessment of the skin lesion is needed, and in these cases, BD is typically found on histology [4].

In Australia, Ogbourne et al. [14] first described the preclinical activity of IM (PEP005, ingenol-3-angelate), a hydrophobic diterpene ester isolated from the plant *Euphorbia peplus*, for the treatment of skin cancer. The same group demonstrated that IM field-directed treatment of UVB-damaged skin reduced tumor lesion formation and removed mutant p53 patches [15]. A recent article elucidated direct effects of IM on primary keratinocytes, patient-derived SCC cells and a SCC cell line [16]. IM thus inhibits viability and proliferation of all keratinocyte-derived cells in a biphasic way – IM-induced cell death is mediated through the PKCδ/MEK/ERK pathway and the downstream induction of IL1R2 and IL13RA2 expression to the reduced viability of IM-treated cells [16]. Longo et al. [17] recently reported 2 cases of non-invasive monitoring of morphological changes in AK treated with IM using a combination of dermoscopy and reflectance confocal microscopy. They concluded that both methods represent a non-invasive possibility to monitor treatment efficacy of this new drug [17].

We describe a case of recurring BD successfully treated with IM gel. A first article [18] reported a case of a 74-year-old man treated with sunitinib, a multi-kinase inhibitor, for metastatic renal cell carcinoma that he had developed together with numerous SCC and 2 BD tumors at his abdomen. He was treated with IM gel 0.05% once daily for 2 days consecutively. The healing was confirmed by histopathological examination, but was only partial in 1 of

the 2 BD tumors. The authors wrote that a second treatment cycle was planned. A second article [19] reported a case of a 79-year-old woman with BD on the right calf. The authors applied IM 0.05% gel on the tumor area once daily for 3 days consecutively, achieving a total remission after 10 weeks, confirmed by histopathological examination and without recurrence 6 months after treatment.

Our patient's BD had developed when she was still under pharmacological immunosuppression with cyclosporine A. Her immunosuppression may well have been an aggravating factor in the numerous recurrences observed. As in the first reported case [18], remission occurred after occlusive use of IM. We thus propose that for recalcitrant or relapsing cases of BD, occlusive treatment with IM may be a promising approach. Serial dermoscopy proved a helpful procedure informing about treatment outcome with early detection of relapse at 6 weeks after the first application of IM and sparing the patient from additional biopsies. We thus believe that dermoscopy is a valuable method for the follow-up of topical treatments in BD treated with IM [3, 4, 11–13, 17].

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Statement of Ethics

Informed consent was obtained from the patient.

Disclosure Statement

C.G. and S.L.-P. declare that they have no conflicts of interest. C.M. is member of the Advisory Board Dermatology for LEO Pharma.

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